Phase separation drives heterochromatin domain formation.

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Authors: Amy R Strom, Alexander V Emelyanov, Mustafa Mir, Dmitry V Fyodorov, Xavier Darzacq, Gary H Karpen

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Public Summary:
Constitutive heterochromatin is an important component of eukaryotic genomes that has essential roles in nuclear architecture, DNA repair and genome stability, and silencing of transposon and gene expression. Heterochromatin is highly enriched for repetitive sequences, and is defined epigenetically by methylation of histone H3 at lysine 9 and recruitment of its binding partner heterochromatin protein 1 (HP1). A prevalent view of heterochromatic silencing is that these and associated factors lead to chromatin compaction, resulting in steric exclusion of regulatory proteins such as RNA polymerase from the underlying DNA. However, compaction alone does not account for the formation of distinct, multi-chromosomal, membrane-less heterochromatin domains within the nucleus, fast diffusion of proteins inside the domain, and other dynamic features of heterochromatin. Here we present data that support an alternative hypothesis: that the formation of heterochromatin domains is mediated by phase separation, a phenomenon that gives rise to diverse non-membrane-bound nuclear, cytoplasmic and extracellular compartments. We show that Drosophila HP1a protein undergoes liquid-liquid demixing in vitro, and nucleates into foci that display liquid properties during the first stages of heterochromatin domain formation in early Drosophila embryos. Furthermore, in both Drosophila and mammalian cells, heterochromatin domains exhibit dynamics that are characteristic of liquid phase-separation, including sensitivity to the disruption of weak hydrophobic interactions, and reduced diffusion, increased coordinated movement and inert probe exclusion at the domain boundary. We conclude that heterochromatic domains form via phase separation, and mature into a structure that includes liquid and stable compartments. We propose that emergent biophysical properties associated with phase-separated systems are critical to understanding the unusual behaviours of heterochromatin, and how chromatin domains in general regulate essential nuclear functions.

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